Clinical and epidemiological characteristics of multiple sclerosis patients receiving disease-modifying treatment in Poland

Katarzyna Kapica-Topczewska[1], Francois Collin[2], Joanna Tarasiuk[1], Monika Chorąży[1],
Agata Czarnowska[1], Mirosław Kwaśniewski[2], Waldemar Brola[3], Halina Bartosik-Psujek[4],
Monika Adamczyk-Sowa[5], Jan Kochanowicz[1], Alina Kułakowska[1]

[1]Department of Neurology, Medical University of Bialystok, Poland

[2]Centre for Bioinformatics and Data Analysis, Medical University of Bialystok, Poland

[3]Faculty of Medicine and Health Sciences, Institute of Physiotherapy, Jan Kochanowski University, Kielce, Poland

[4]Neurology Clinic with Brain Stroke Sub-Unit, Clinical Hospital No. 2 in Rzeszow, Medical Faculty, University of Rzeszow, Poland

[5]Department of Neurology in Zabrze, Medical University of Silesia, Zabrze, Poland

ABSTRACT

Aim of study. The aim of this study was to collect and analyse data on relapsing-remitting multiple sclerosis (RRMS) patients receiving disease-modifying therapies (DMTs) in Poland.

Material and methods. This observational, multicentre study with prospective data collection included RRMS patients receiving DMTs reimbursed by the National Health Fund (NFZ) in Poland, monitored by the Therapeutic Programme Monitoring System (SMPT). Demographic profiles, disability status, and treatment modalities were analysed.

Results. Data from 11,632 RRMS patients (from 15,368 new prescriptions) was collected including 10,649 patients in the first-line and 983 in the second-line therapeutic programme of DMTs. The proportion of females to males was 2.39 in the first-line and 1.91 in the second-line. The mean age at DMTs start was 36.6 years in the first-line and 35.1 in the second-line. The median time from the first symptoms to MS diagnosis was 7.4 months, and from MS diagnosis to treatment it was 18.48 months. A total of 43.4% of MS patients started DMT during the 12 months following diagnosis. There was a positive correlation between the duration from MS diagnosis to the start of DMT and a higher initial EDSS value [correlation 0.296 (p < 0.001)]. About 10% of patients stopped DMTs. In Poland, about one third of all MS patients are treated in both lines of therapeutic programmes, and the choice of first-line treatment depends on the region of the country.

Conclusions. In Poland there is a need to increase MS patient access to DMTs by improving the organisation of therapeutic programmes.

Key words: multiple sclerosis, disease-modifying therapies, Poland, drug programmes

(*Neurol Neurochir Pol 2020; 54 (2): 161–168*)

Introduction

Multiple sclerosis (MS) is a chronic inflammatory de-myelinating disease of the central nervous system leading to oligodendrocyte degeneration and neuron destruction. MS affects mainly young adults and is a leading cause of long-term disability. The estimated number of people suffering from MS worldwide is approximately 2.3 million [1, 2]. In Poland, there are around 45,000 patients, with a prevalence of approximately 110–115/100,000 residents [3, 4].

In Poland, disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) patients are

reimbursed by the National Health Fund (NFZ) and monitored by the Therapeutic Programme Monitoring System (*System Monitorowania Programów Terapeutycznych*- SMPT), available online on the NFZ website.

The purpose of this study was to collect and analyse data on the demographic profiles, diagnostic and treatment modalities in patients with RRMS receiving DMTs in the first-line and second-line programmes reimbursed by the NFZ, treated in all MS centres in Poland.

Material and methods

This observational, multicentre study with prospective data collection was performed in all RRMS patients treated with DMTs, diagnosed according to McDonald's 2010 criteria. The first- and second-line drug programmes were initiated in 2004 and 2013, respectively. Data from patients treated in the drug programmes was collected prospectively in SMPT from 2014 to January 2018. SMPT is a programme available on the NFZ website, which is used to maintain electronic documentation of the implementation and monitoring of drug programmes. SMPT records and stores information about Polish RRMS patients from 128 MS treatment centres for the first-line, and from 59 centres for the second-line.

The first-line treatment includes: interferon beta (IFNβ) since 2004, glatiramer acetate (GA) since 2005, pegylated interferon beta (PEG) and dimethyl fumarate (DMF) since 2016, teriflunomid (TER) and alemtuzumab (ALE) since 2017. The IFNβ drug group includes subcutaneous and intramuscular IFNβ 1a and subcutaneous IFNβ 1b.

Within the second-line treatment, two drugs are available: natalizumab (NAT) and fingolimod (FTY), both since 2013.

The RRMS patients are included in the NFZ drug programmes according to clear rules. In the first-line programme, patients must have experienced at least one relapse or have shown at least one new gadolinium (GD+) lesion on MRI in the preceding 12 months before qualification. An Expanded Disability Status Scale (EDSS) score of less than 5.0 points is also needed. Changing drugs within the first-line is allowed in the case of adverse effects or partial treatment failure. For patients in whom first-line therapy is ineffective, second-line treatment is indicated.

To become qualified to the second-line, patients must meet the following criteria: no response to a complete cycle (lasting a minimum of 12 months) of the first-line DMT, defined as the fulfilment of both these two conditions:

1: two or more moderate relapses requiring administration of steroids (an increase of 1–2 points in EDSS score) or one severe relapse after six months of treatment (an increase in EDSS score higher than 2 points)

and

2: new lesions on MRI (minimum two GD+ lesions or minimum three new T2- lesions) performed every 12 months of therapy.

In rapidly evolving severe relapsing remitting MS (RES MS), NAT has been administered since 2013 and ALE since 2017; FTY for RES MS was not funded until 2018. To be treated as RES MS, patients must have active disease and the disease activity must meet both clinical and radiological criteria, the same as in the second-line treatment programme.

After each 12 months of treatment in both drug programmes, an evaluation of the treatment efficacy, which determines whether a patient can continue on the treatment or should be switched to another drug, is carried out. DMTs should be discontinued in cases of secondary progressive MS development.

In the first-line programme, the clinical and radiological disease activity evaluations carried out every 12 months while on treatment allowed us to distinguish five groups of MS disease activity:

— Group 0: no substantial clinical and radiological signs of disease activity
— Group A: 1 new T2 or 1 new GD+ lesion and 1 relapse
  Group B: 2 new T2 or 1 new GD+ and 1 relapse with EDSS worsening ≥ 1.0
— Group C: 2 new T2 or 1 new GD+ and 2 relapses with EDSS worsening ≥ 1.0
— Group D: 3 new T2 or 2 new GD+ and 2 new relapses with EDSS worsening ≥ 1.0

Our study was approved by the Regional Medical Ethics Committee (the Medical University of Bialystok). Written consent to use the data for scientific research was obtained from the President of the NFZ. Every patient undertaking treatment reimbursed by NFZ consented to the collection of data in SMPT. We received anonymous data from the NFZ, thus preventing identification of the patients.

Statistical analysis

The data provided by the NFZ corresponded to drug monitoring records. For the analysis, a prescription corresponded to the uninterrupted period of time during which a patient received a specific DMT drug was used. From the records, every combination of patient and DMT start date constituted the prescription presented in Table 1. Each evaluation was described by patient characteristics (sex, age at DMT start, duration from first symptoms to diagnosis, duration from diagnosis to DMT start, EDSS, MS centre, drug name, treatment line, DMT start date), and follow-up (duration in months). A descriptive analysis of the DMTs was carried out to provide a general characterisation of DMT, and time evolution of DMT use. In addition, regional variations were studied in terms of disease prevalence (2017 census data for population size), and variation in first-line DMT choices. Evaluation of the clinical and radiological disease activity was run by the comparison of record pairs delimiting periods of 12 months. Evaluation relied on the estimation of the following responses: number of relapses, number of relapses with EDSS worsening over 1 point, number of new T2 lesions, and number of new GD+ lesions.

Table 1. Patient characteristics

| Line | Prescriptions | | | Median duration in months | | Evaluations | Evaluat. started within 12 months from diagnosis (%) | Age at evaluat. start | | EDSS at evaluat. start (median) | Number of patients (2017-12-31) |
	DMT	n	F:M	Symptoms to diagnosis	Diagnosis to treatment			mean	median		
I line		14259	2.39	7.7	14.82	13.63	46.4	36.6	36	1,5	10649
	INF	9030	2.37	7.3	8.25	25.07	55.9	36.2	35	1,5	6561
	GA	2777	2.47	8.1	29.67	12.16	31	37.5	37	2	1983
	DMF	2150	2.32	8.3	38.54	0	29.8	36.8	36	2	1873
	TER	71	2.55	16.1	67.84	0	7	43.6	45	2	48
	PEG	224	2.73	7.95	44.76	0	28.6	39.4	39.5	2	177
	ALZ	7	2.5	9.2	41.86	0	0	39.9	40	4,5	7
II line		1109	1.91	5	65.54	22.7	3.6	35.1	34	3	983
	FTY	724	1.77	5	65.25	23.69	0.7	35.5	34	3	643
	NAT	385	2.21	5	68.04	12.71	9.1	34.3	33	3,5	340
ALL		15368	2.35	7.4	18.48	13.96	43.3	36.5	36	2	11632

DMT — disease modifying therapies; n — number; F — female; M — male; INF — interferon beta; GA — glatiramer acetate; DMF — dimethyl fumarate; TER — teriflunomid; PEG — pegylated interferon beta — ALE — alemtuzumab; FTY — fingolimod; NAT — natalizumab; Evaluat — evaluation; EDSS — Expanded Disability Status Scale

This allowed us to estimate MS disease activity category as being in Group 0, Group A, Group B, Group C or Group D.

Results

Data from 11,632 MS patients was collected (including 15,368 prescriptions). Of these, 10,649 patients (14,259 prescriptions) were in the first-line and 983 patients (1,109 prescriptions) were in the second-line therapeutic programme of DMTs. The proportion of females to males was 2.39 in the first-line and 1.91 in the second-line. A significantly higher percentage of men was treated in the second-line programme than in the first-line (+1.5 to +2% - significant Chi2 independence test). The mean age at DMTs start was 36.6 years in the first-line and 35.1 in the second-line. The median time from the first symptoms to MS diagnosis was 7.4 months, and from MS diagnosis to treatment was 18.48 months. A total of 43.4% of MS patients started DMT during the 12 months from diagnosis. Patient characteristics are presented in Table 1.

There was a positive correlation between the duration from MS diagnosis to the start of DMT and disability progression. The longer the time taken to start treatment, the higher the initial EDSS value (correlation 0.296 (p < 0.001). Median EDSS at initiation of the first-line therapy was 1.5, and 3.0 at initiation of the second-line therapy.

During the study, 368 patients (35% of all subjects treated in the second-line) from the first-line were switched to the second-line because of the ineffectiveness of the first-line DMTs. The rest of the patients in the second-line were those with RES MS or ones who continuing treatment after participating in clinical trials. The first-line therapies that were the most frequently switched to the second-line were IFNβ (61% of all escalations to the second-line) and GA (33.7% of all escalations to the second-line). A total of 10% of patients from the first-line and 8% from the second-line stopped the DMTs. In the first-line, the most common causes for aborting treatment were lack of treatment efficacy (44.9%), and patient resignation (34.3%). In the second-line they were patient resignation (40%), lack of treatment efficacy (27.1%), and adverse events (27.1%) (Fig. 1).

Poland is divided into 16 voivodeships (provinces), which differ in their number of inhabitants and population density. Taking into account the number of inhabitants in individual voivodeships, the largest percentage of patients received DMTs in *mazowieckie, łódzkie, małopolskie, wielkopolskie*, and *świętokrzyskie*. The smallest number of patients received MS treatment in *lubuskie, warmińsko-mazurskie, zachodniopomorskie*, and *podlaskie*. The number of patients treated in individual voivodeships in relation to the number of all inhabitants is shown in Figure 2. The choice of first-line treatment depended on the region of the country. *Opolskie* and *małopolskie* had higher use of DMF, *podkarpackie* and *dolnośląskie* had higher use of interferon beta. Geographically close regions had similar first DMTs choice (for example

śląskie, małopolskie, opolskie) (Fig. 3). A similar analysis was performed in the second-line programme, but no geographical differences in treatment preferences were shown.
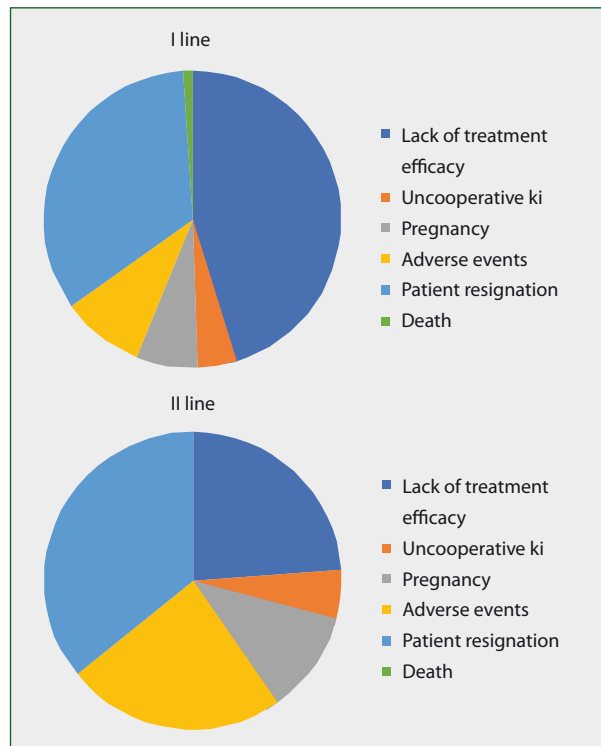
The number of new first-line DMTs prescriptions, recorded within the SMPT, increased every year. It was negligible before 2009, low until 2011, substantial and stable between 2012 and 2014, and has increased greatly since then. INFβ was the main drug from 2009 to 2016. The introduction of DMF in MS therapy (2016) was associated with a reduction of INFβ treatment, while other new DMTs remained marginally used (PEG, TER, ALZ). GA has been the second most used DMT, relatively stable, representing approximately 20% of new prescriptions every year. The use of second-line DMTs has remained stable since their introduction in 2013, with about one third of patients treated with NAT and two thirds with FTY (Fig. 4, 5).

The results of the analysis of clinical and radiological disease activity in the first-line programme are presented in Table 2. The annual evaluations comparing current evaluation to the preceding evaluation allowed 24,872 MS disease activity assessments, of which 7,780 were obtained after 12 months of treatment. After a year of treatment, the vast majority of patients did not report MS disease activity (7,410 observations, i.e. 95% of patients at that time). 370 reported MS disease activity, and only 0.4% were eligible to the second-line treatment (30 patients in MS disease activity category D). The number of evaluations decreased with time (Table 2), and the proportion of any MS disease activity was relatively stable: 91–96% of patients did not report any MS disease activity during the year (2–4% evidenced categories A and B, while less than 1% corresponded to categories C and D). Therefore, a small number of RRMS patients with MS disease activity, while on the first-line of DMTs treatment, met the restrictive criteria to qualify to the second-line (Group D in Tab. 2).

Figure 1. Causes for aborting DMTs treatment in first and second-line drug programmes
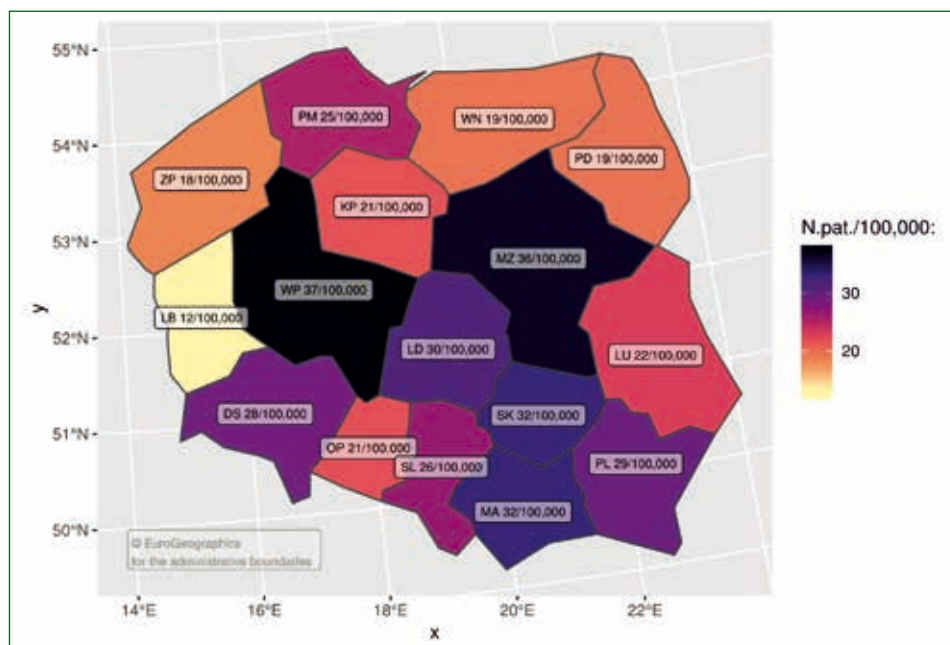
Figure 2. Number of new prescriptions of DMTs in individual voivodeships in relation to total number of inhabitants
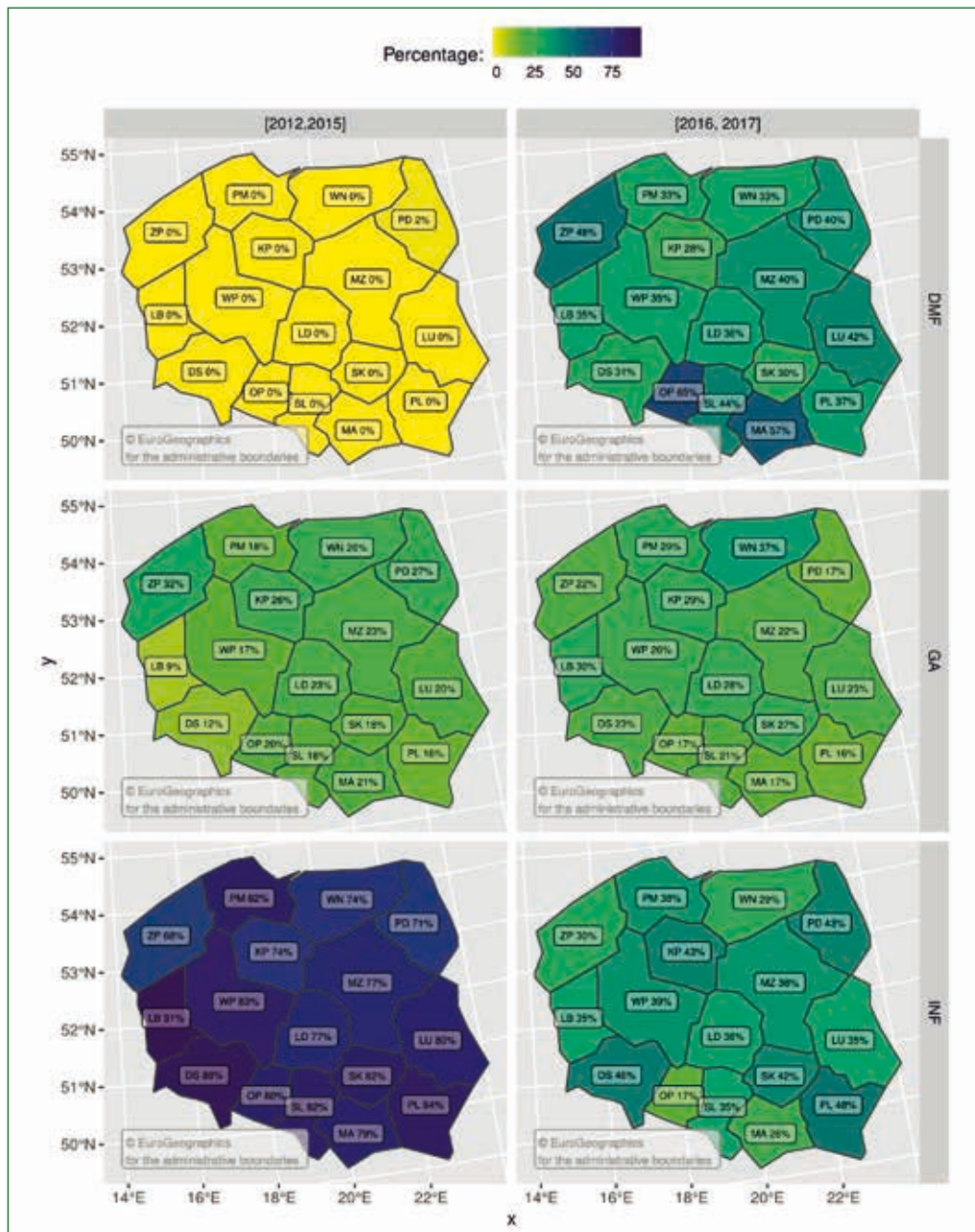
**Figure 3.** Regional differences in prescriptions of INF, GA and DMF from 2012 to 2017

Discussion

Real-life MS population studies are powerful tools for providing meaningful information on disease epidemiology, the social and economic impact of the disease, and medication effectiveness. Real-world data helps the national regulatory authorities to improve the quality of care of MS patients and to make relevant decisions about healthcare programmes [5].

This study is the first one to have enrolled all RRMS patients treated with DMTs reimbursed by the NFZ in Poland. The mean age of participants and the sex ratio are similar to previously reported observations from Poland and other

countries [1–10]. Interestingly, we found that a significantly higher percentage of men was treated in the second-line programme than in the first-line. Analysis of the MSBase registry showed that men with RRMS had faster and shorter time-to--EDSS points 3 and 6 compared to women [11]. It has also been shown that men are more likely to develop more severe relapses with a relatively higher risk of incomplete remission; women are more prone to have relapses, but they are also relatively more likely to recover completely [11].

Compared to previous studies, we found a slightly shorter interval between the occurrence of the first symptoms and MS diagnosis [3, 4, 6]. The diagnostic process is probably quicker
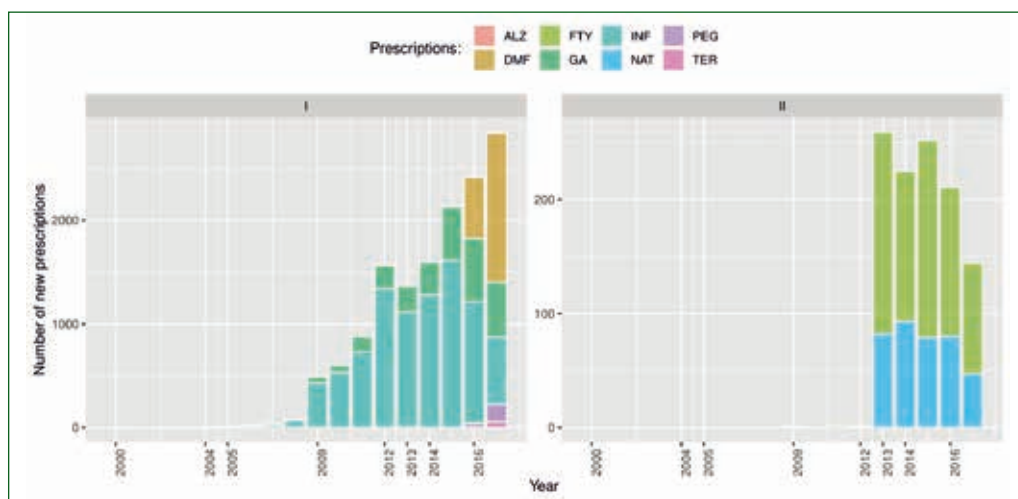
Figure 4. Number of new prescriptions of DMTs in first and second-line drug programmes
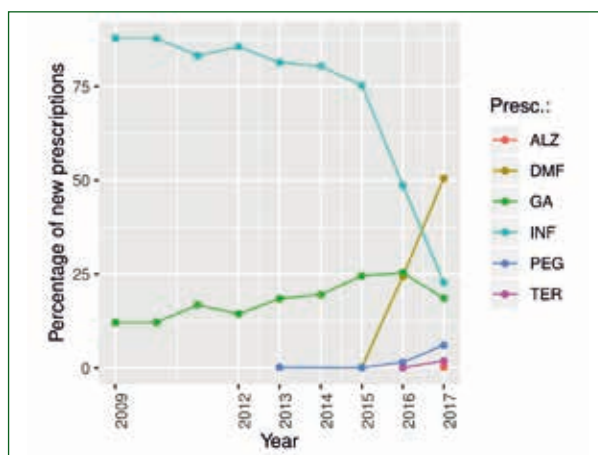
Figure 5. Percentage of new prescriptions of DMTs in first-line drug programme

due to more efficient use of the McDonald diagnostic criteria, better access to MRI, and increased awareness among physicians about the course of MS and the possibilities for early treatment [12]. In our study, the median time from MS diagnosis to start of the first DMT was 14.8 months, and in 43.3% of patients the first DMT had begun within 12 months of diagnosis. The value of the median time from diagnosis to start of the first DMT was probably increased by the inclusion of patients with benign MS to the first-line programme. According to the rules (i.e. patients must experience at least one relapse or have at least one GD+ lesion on MRI in the preceding 12 months), some patients with benign RRMS are included into the programme many years after diagnosis. In our study, the longest time from diagnosis to the initiation of the first DMT was 45.7 years.

We should take into account that in patients with RRMS it is important to start DMTs as early as possible, because the

Table 2. Number of completed evaluations of any MS disease activity category

Category	Months								Σ
	12	18	24	30	36	42	48	51+	
0	7410	867	4013	705	2962	656	2334	4791	23738
A	180	34	94	19	57	14	45	83	526
B	158	42	98	19	69	9	35	66	496 17
C	2	1	3	1	3	0	0	7	95
D	30	4	19	1	12	2	10	17	
Σ	7780	948	4227	745	3103	681	2424	4964	24872

Number of complete evaluations regarding MS disease activity category (0: no substantial clinical or radiological signs of disease activity; A: 1 new T2 or 1 new GD+ lesion and 1 relapse; B: 2 new T2 or 1 new GD+ and 1 relapse with EDSS worsening ≥ 1.0; C: 2 new T2 or 1 new GD+ and 2 relapses with EDSS worsening ≥1; D: 3 new T2 or 2 new GD+ and 2 new relapses with EDSS worsening ≥ 1) and number of months. E.g. 94 annual evolutions were categorised as MS disease activity A, 24 months after the prescription started (± 3 months, therefore between 21 and 27 months). Σ — number of evaluations (evaluation visits) of any category (column margin) and at any given time (row margin)

treatment is most effective in the early stages of the disease. In our study, we found that a longer time from MS diagnosis to start of treatment was related to a higher initial EDSS value. Moreover, recent studies have shown that in active MS patients treated with NAT or FTY, a baseline EDSS of less than 3.0 increased the probability of remaining disease activity-free [13–16]. It was also found that initial treatment with highly effective therapies, compared to initial treatment with injectable agents, was associated with a lower risk of conversion to secondary progressive MS [17]. In our study, the baseline EDSS at the beginning of treatment in the second-line programme was 3.0.

It is undeniable that Polish RRMS patients start DMTs, especially second-line medications, too late. In Poland in January 2018 only 8.8% of all patients were being treated in the second-line programme, because only a small group of patients met the restrictive criteria of the second-line drug programme. In 2013, in Norway 39%, in Sweden 31.8%, in Denmark 29.5%, and in France about 20% of MS patients were being treated with second-line medications [18]. In our study, IFNβ and GA were more frequently switched to the second-line therapies because of the ineffectiveness than first-line oral medications, but this finding may be related to the fact that first-line injectable drugs were used much longer in the drug programme (> 4 years) than oral ones (< 2 years). INFβ has been the main DMT used until 2016. For example in 2015, 75% of MS patients in the first-line were treated with INFβ. But in 2017, DMF was the most common drug used in MS therapy. On the other hand, GA has been used at a constant rate of between 12% and 25% of first-line MS therapy.

Clinical and radiological analysis of disease activity, done in our study, showed that more patients with MS disease activity may be switched from the first-line to the second-line, if less restrictive criteria of therapy escalation are used. According to the new ECTRIMS/EAN, in the case of the presence of early disease activity (i.e. relapses and/or disability progression and/or MRI activity at 6/12 months), a more efficacious drug should be offered to MS patients who are treated with injectable agents [19].

In addition, in Poland a delay in reimbursement of innovative therapies is observed. In our country, the time between medication approval by the European Medicines Agency and drug reimbursement is more than 15 months. For comparison, that time is less than three months in Bulgaria, Germany, Italy, Lithuania, Malta, and Norway [20].

The most prosperous voivodeships (*mazowieckie, wielkopolskie, małopolskie*) are the ones with the highest populations and highest proportions of MS patients receiving DMTs. Interestingly, we found that the choice of the first-line treatment depends on the region. Geographically close regions had similar drug choices even though all MS centres in Poland have the same drug programmes. No evidence-based criteria exist to inform the choice among different first-line DMTs.

The choice of first therapy is challenging and depends on the neurologist's and patient's preferences.

In Poland, the rate of MS prevalence is approximately 110–115/100,000 residents [3, 4]. Taking into account the results obtained in this study, it can be assumed that in our country there are about 45,000 MS patients. This means that in January 2018 in Poland, about one third of all MS patients were being treated in both DMT line programmes. According to BAROMETER 2015, the total population of RRMS patients treated with DMTs was 80% in Austria, Sweden, and Switzerland; 70% in Belgium and France; and 65% in Greece [20]. In Germany (in 2013), 69% of MS patients received DMTs [18, 21]. These differences are mainly a consequence of wealth inequality across the European countries and the impact of DMTs on health budgets. Additionally, limited access to immunomodulatory therapy in Poland is associated with the restrictive reimbursement criteria established by the NFZ and the low efficiency of MS centres, which is partly due to a lack of neurologists and MS nurses.

Conclusions

This is the first observational, multicentre study with prospective data collection analysing diagnostic and treatment modalities and the demographic profile of all RRMS patients receiving DMTs reimbursed by the NFZ in Poland. The results show that about one-third of all Polish MS patients are treated with DMTs. Our study highlights the long interval between disease diagnosis and DMTs initiation, and the low percentage of patients treated with second-line medications. It is necessary to increase the access of MS patients to DMTs by improving the organisation of the drug programmes.

Acknowledgements

References

1. Atlas of MS 2013: Mapping Multiple Sclerosis Around the World. London: Multiple Sclerosis International Federation. 2013.

2. Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology. 2014; 83(11): 1022–1024, doi: 10.1212/WNL.0000000000000768, indexed in Pubmed: 25200713.

3. Brola W, Sobolewski P, Flaga S, et al. Prevalence and incidence of multiple sclerosis in central Poland, 2010-2014. BMC Neurol. 2016; 16(1): 134, doi: 10.1186/s12883-016-0662-8, indexed in Pubmed: 27516084.

4. Kapica-Topczewska K, Brola W, Fudala M, et al. Prevalence of multiple sclerosis in Poland. Mult Scler Relat Disord. 2018; 21: 51–55, doi: 10.1016/j.msard.2018.02.016, indexed in Pubmed: 29455075.

5. Trojano M, Bergamaschi R, Amato MP. et. al. Italian Multiple Sclerosis Register Centers Group. The Italian multiple sclerosis register. Neurol Sci. 2019; 40(1): 155–165.

6. Kułakowska A, Bartosik-Psujek H, Hożejowski R, et al. Selected aspects of the epidemiology of multiple sclerosis in Poland - a multi-centre pilot study. Neurol Neurochir Pol. 2010; 44(5): 443–452, doi: 10.1016/s0028-3843(14)60134-1, indexed in Pubmed: 21082490.

7. Pierzchala K, Adamczyk-Sowa M, Dobrakowski P, et al. Demographic characteristics of MS patients in Poland's upper Silesia region. Int J Neurosci. 2015; 125(5): 344–351, doi: 10.3109/00207454.2014.937002, indexed in Pubmed: 24946203.

8. Grytten N, Aarseth JH, Lunde HMB, et al. A 60-year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland County, Western Norway. J Neurol Neurosurg Psychiatry. 2016; 87(1): 100–105, doi: 10.1136/jnnp-2014-309906, indexed in Pubmed: 25714916.

9. Westerlind H, Boström I, Stawiarz L, et al. New data identify an increasing sex ratio of multiple sclerosis in Sweden. Mult Scler. 2014; 20(12): 1578–1583, doi: 10.1177/1352458514530021, indexed in Pubmed: 24842964.

10. Kingwell E, Zhu F, Marrie RA, et al. High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (1991-2010). J Neurol. 2015; 262(10): 2352–2363, doi: 10.1007/s00415-015-7842-0, indexed in Pubmed: 26205633.

11. Kalincik T. Multiple Sclerosis Relapses: Epidemiology, Outcomes and Management. A Systematic Review. Neuroepidemiology. 2015; 44(4): 199–214, doi: 10.1159/000382130, indexed in Pubmed: 25997994.

12. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018; 17(2): 162–173, doi: 10.1016/S1474-4422(17)30470-2, indexed in Pubmed: 29275977.

13. Izquierdo G, Damas F, Páramo MD, et al. The real-world effectiveness and safety of fingolimod in relapsing-remitting multiple sclerosis patients: An observational study. PLoS One. 2017; 12(4): e0176174, doi: 10.1371/journal.pone.0176174, indexed in Pubmed: 28453541.

14. Agius M, Meng X, Chin P, et al. Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom. CNS Neurosci Ther. 2014; 20(5): 446–451, doi: 10.1111/cns.12235, indexed in Pubmed: 24684973.

15. Trojano M, Butzkueven H, Kappos L, et al. Tysabri® Observational Program (TOP) Investigators. Natalizumab treatment shows low cumulative probabilities of confirmed disability worsening to EDSS milestones in the long-term setting. Mult Scler Relat Disord. 2018; 24: 11–19, doi: 10.1016/j.msard.2018.04.020, indexed in Pubmed: 29860197.

16. Cobo-Calvo Á, Bau L, Matas E, et al. Effectiveness of natalizumab in patients with highly active relapsing remitting multiple sclerosis. Eur Neurol. 2015; 73(3-4): 220–229, doi: 10.1159/000375371, indexed in Pubmed: 25792347.

17. Brown JW, Coles A, Horakova D, et al. MSBase Study Group. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. JAMA. 2019; 321(2): 175–187, doi: 10.1001/jama.2018.20588, indexed in Pubmed: 30644981.

18. Wilsdon T, Barron A, Mitchell-Heggs A, et al. Access to medicines for multiple sclerosis: challenges and opportunities. CRA Project No. D19380.

19. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Eur J Neurol. 2018; 25(2): 215–237, doi: 10.1111/ene.13536, indexed in Pubmed: 29352526.

20. Barometr MS 2015. European Multiple Sclerosis Platform Barometr 2015.

21. Berger T, Adamczyk-Sowa M, Csépány T, et al. Management of multiple sclerosis patients in central European countries: current needs and potential solutions. Ther Adv Neurol Disord. 2018; 11: 1756286418759189, doi: 10.1177/1756286418759189, indexed in Pubmed: 29511382.